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## Isotopic Polymorphism in Pyridine†\*\*

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<sup>[†]</sup>We dedicate this paper to Dr Frank Allen on the occasion of his retirement as Executive Director of the Cambridge Crystallographic Data Centre.

### Supporting information:

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author. Crystallographic information files can be obtained from the Cambridge Crystallographic Data Centre, quoting deposition numbers CCDC 695956 – 695959. A summary table of crystal data is also given in the *Supporting Information*.

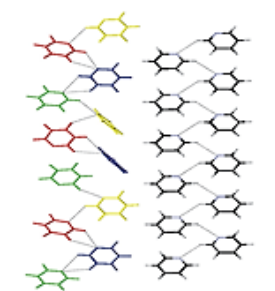
### Keywords:

Polymorphism; Crystal Engineering; Crystal Growth; High Pressure Chemistry; Isotope Effects

## Synopsis

It is normally assumed that deuteration has only a minor effect on the stabilities of crystal structures. This assumption is wrong for pyridine. A low-temperature polymorph exists for pyridine-d<sub>5</sub>, but not for pyridine-h<sub>5</sub>, adding a further twist to the already unusual structural chemistry of one of the simplest and most familiar laboratory chemicals.

## Graphical abstract



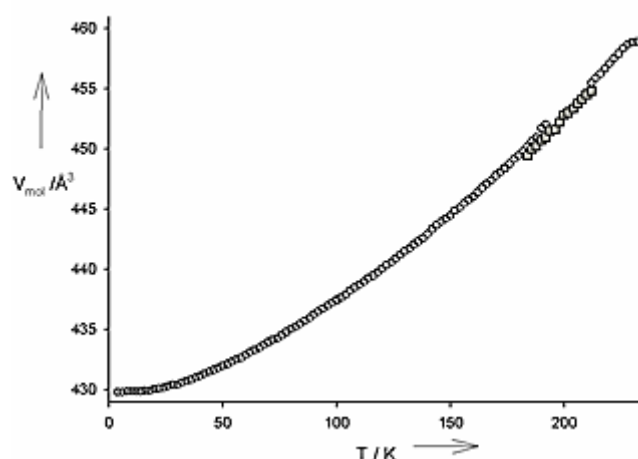
## Abstract

The *ab initio* calculation of the relative stabilities of isomers of gas phase molecules rates as one of the outstanding scientific achievements of the twentieth century. Our understanding of the structure of solid state is, by comparison, much less well advanced. The problem is illustrated by the crystal structure of pyridine. Pyridine (C<sub>5</sub>H<sub>5</sub>N or ‘h<sub>5</sub>’ hereafter) is one of the simplest heteroaromatic compounds but its crystal structure (phase h<sub>5</sub>-I) is unusually complicated, having four independent molecules in the asymmetric unit ( $Z' = 4$ ).<sup>[1]</sup> Price *et al.* have surveyed the potential for polymorphism in pyridine using *ab initio* crystal structure prediction methods, finding over a dozen crystal structures that were energetically competitive with h<sub>5</sub>-I.<sup>[2]</sup>

In parallel with Price’s theoretical work an intense experimental search was made by one of us (RB group) for new low-temperature polymorphs of pyridine. Though all attempts to crystallize h<sub>5</sub> failed to yield anything but the h<sub>5</sub>-I phase, crystallization of pyridine-d<sub>5</sub> (d<sub>5</sub>) from pentane yielded a new phase, d<sub>5</sub>-II, at 188 K. Recrystallization from a low-melting solvent such as pentane has been shown in the past to circumvent high-temperature phases because saturation of the solution occurs below the temperature of the phase transition.<sup>[3]</sup> The new d<sub>5</sub>-II phase has one molecule in the asymmetric unit ( $Z' = 1$ ), but does not correspond to any of the predicted polymorphs of h<sub>5</sub>.

The effect of temperature on the crystal structure of pyridine-d<sub>5</sub> was subsequently investigated further using neutron powder diffraction. The sample was ground at 77 K<sup>[4]</sup> and then rapidly cooled to 2 K. The powder pattern was successfully modelled as d<sub>5</sub>-I (see Fig. S1a in the Supplementary Information). The sample was then warmed in steps of 2 K, with patterns being acquired at each temperature. When the sample reached 170 K it began to undergo a sluggish phase transition into d<sub>5</sub>-II. After collecting a clean d<sub>5</sub>-II neutron powder

diffraction data set suitable for structure refinement at 195 K (Fig. S1*b*), the sample was again warmed in 2 K steps, collecting powder patterns at each stage. At 215 K the sample transformed *back to* d5-I, remaining in this phase until it melted at 230 K. The two transitions are clearly seen in a plot of molecular volume against temperature (Fig. 1).



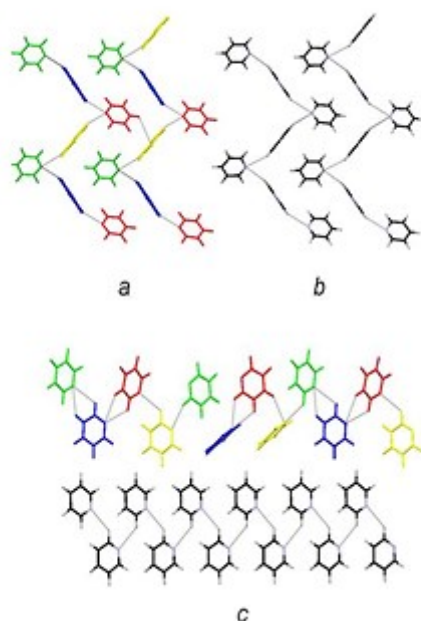
**Figure 1.** Molecular volume versus temperature for pyridine-d<sub>5</sub>. The open circles and filled squares correspond to phases d5-I and d5-II, respectively. Data obtained by Pawley-fitting of neutron powder diffraction patterns.

The phase transitions observed by diffraction were investigated further using calorimetry. A sample of pyridine-d<sub>5</sub> was quenched at 80 K and the heat capacity measured from 80 K to 300 K. Exothermic and endothermic events appeared with on-sets near 170 K (d5-I→d5-II) and 215 K (d5-II→d5-I), respectively, consistent with the neutron powder experiments. However, when a sample was first allowed to anneal at 200 K for 12 h, only the endothermic event at 215 K was observed. These results are supported by single-crystal X-ray diffraction: a crystal of phase d5-I grown at 220 K could be rapidly cooled to 150 K without any phase transition. Warming the sample from 150 K to 195 K generated a twinned crystal of phase d5-II, which could be cooled to 100 K without transforming back into phase d5-I.

Combining these results shows that that d5-I becomes metastable on cooling below 215 K. It can be transformed to the stable phase (d5-II) by first cooling below 170 K and then increasing the temperature into the range 170-215 K. Between 215 K and the melting point d5-I is the stable form. The data in Fig. 1 might be mistakenly taken to show that d5-II has a ‘window of stability’ bounded either side by d5-I. While such behaviour has been seen in malonitrile,<sup>[5]</sup> in pyridine the formation of phase d5-I on rapid cooling of the liquid phase is a kinetic effect, and below 215 K d5-II is the thermodynamically stable phase.

The only way that we have found to obtain d5-II directly from a liquid phase by cooling is the way we first obtained it, from a 1:1 mixture of pyridine-d<sub>5</sub> and pentane. While similar experiments applied to h5 consistently failed to yield anything but h5-I, we have shown that both h5-II and d5-II may be obtained at high pressure (1.1 GPa). Though it is usually neglected at ambient conditions, the pressure  $\times$  volume term strongly influences enthalpy and free energy differences between phases at elevated pressures. The lower molecular volume in phase-II relative to phase-I is clearly shown in Fig. 1, and the h5-II would thus be expected to become more stable at high pressure.

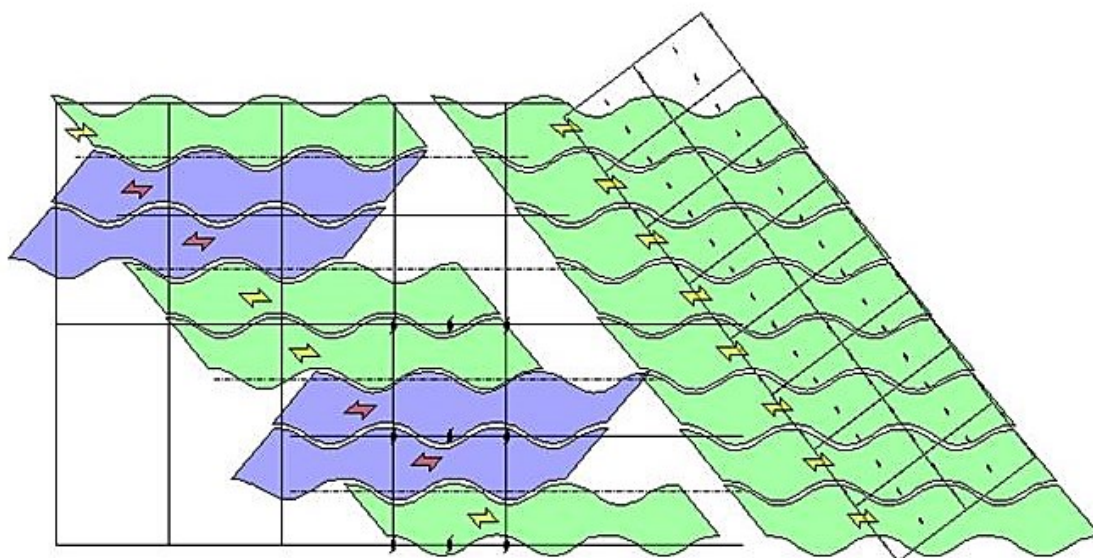
The structural relationship between phases-I and II can be seen by recognizing that both polymorphs contain layers which lie parallel to the (100) planes in phase-I and the (110) planes in phase-II (Fig. 2 *a, b*). The most prominent interactions in both phases are CH...N and CH... $\pi$  contacts. PIXEL calculations<sup>[6]</sup> show that the energies of the CH...N and CH... $\pi$  interactions are similar, 8-10 kJ mol<sup>-1</sup>, and during the transition from form II to I some CH...N contacts between the layers are replaced by CH... $\pi$  contacts as the result of changes in the orientations of the molecules (Fig. 2*c*).



**Figure 2.** The relationship between the crystal structures of pyridine I and II. Layers are formed in pyridine-I perpendicular to the (100) planes (*a*), while in pyridine-II similar layers lie parallel to the (110) planes (*b*). The four crystallographically independent molecules in phase-I have been color-coded in (*a*). (*c*) Stacking of the molecules perpendicular to the planes shown in (*a*) and (*b*); notice that the CH... $\pi$  interaction in the middle of the phase-I chain (top) is converted into a CH...N contact in phase-II. CH...N contacts less than 3 Å are shown.

The surface of the layers shown in Figs 3 *a* and *b* are formed into bumps and hollows by the pyridine molecules; on stacking the bumps of one layer fit into the hollows of the next layer. This is shown in ‘cartoon’ form in Fig. 3; a conventional packing diagram in the same orientation as Fig. 3 is available in the supplementary material (Fig. S2). To understand the relationship between phases-I and II we first have to distinguish between two types of layer. One layer (shown in green in Fig. 3) is common to both phases, while the other (shown in blue) is mirror-related to the first layer and only occurs in phase-I. The blue layers are generated from the green ones by glides, which are present in space group  $Pna2_1$ , but absent in  $P2_12_12_1$ . The blue ‘mirror-layers’ still form bumps and hollows, which fit into the surface of the original (green) partner. According to this scheme exact overlap is achieved in phase-I for layers 1 and 5, 2 and 6 *etc.*, so that the unit cell has four times the volume of phase-II, requiring four molecules in the asymmetric unit.

Pyridine therefore shows the unusual property of isotopic polymorphism, and our results are consistent with i.r. spectroscopic measurements carried out forty years ago.<sup>[7]</sup> Other systems exhibiting isotopic polymorphism have recently been listed by Harbison,<sup>[8]</sup> and include co-crystal of 4-methylpyridine and pentachlorophenol, potassium dihydrogen phosphate, ammonium dihydrogen phosphate and arsenate and chromium hydroxide oxide. It seems rare for organic or molecular compounds, and although isotopic substitution changes spectroscopic and kinetic properties of materials, the assumption is usually made that it has little effect on the stabilities of crystal structures. While this is supported by a recent survey of pairs of normal and deuterated small molecule crystal structures,<sup>[9]</sup> our results indicate that the assumption is wrong for pyridine.



**Figure 3.** Cartoon illustrating the layer-stacking schemes in phases I (left) and II (right). Blue and green layers are related by glide operations which are present in phase-I, but absent in phase-II.

Isotopic polymorphism has been described for the co-crystal of 4-methylpyridine and pentachlorophenol (4MPPCP).<sup>[10, 11]</sup> The crystal structure of 4MPPCP with a normal isotropic composition is triclinic, showing a strong OH...N H-bond. Replacement of the H-bond forming H-atom with D (4MPPCP-d<sub>1</sub>) leads to a monoclinic structure. It has been suggested,<sup>[8, 11]</sup> with support from solid state NMR and inelastic neutron scattering experiments, that the H and D zero point energies (ZPEs) of the triclinic form are straddled by the ZPEs of the monoclinic form. The monoclinic structure is stable for the deuterated form, whereas the triclinic structure is favored for the protiated form. If a similar straddling pattern applies for pyridine, the sequence of phases according to their decreasing ZPE is: h5-II, h5-I, d5-I and d5-II. To summarize: the most stable phases we observe are h5-I and d5-II. d5-I is only observed above 215 K, below 215 K it is merely metastable and the transformation from phases I to II is slow. Phase h5-II is less stable than h5-I at all temperatures and, though it is never observed at ambient pressure, it can be formed at high pressure.

The importance of isotopic substitution lies in its relevance to the understanding of polymorphism. Polymorphism is the existence of different arrangements of the same molecule in the solid state. Isotopic substitution is the smallest possible modification of a molecule, yet this can yield polymorphs for systems which are otherwise monomorphic. The dynamical changes attendant on isotopic substitution, which lead to a temperature-dependent variation in the size difference between H and D, have recently been described by Dunitz and Ibberson for benzene.<sup>[12]</sup> In pyridine they lead to formation of different polymorphs. Such examples of isotopic polymorphism under varying conditions of temperature and pressure will form particularly sensitive test cases when dynamics are introduced into crystal structure prediction methodologies.

## Experimental Section

*Low-temperature single crystal X-ray study of d5-II:* Phase d5-II was crystallized at 188 K from a 1:1 mixture of pyridine-d<sub>5</sub> and pentane; crystal data at 158 K in  $P2_12_12_1$ :  $a = 5.5960(17)$ ,  $b = 6.961(2)$ ,  $c = 11.493(3)$  Å,  $V = 447.7(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_{\text{calc}} = 1.174$  g cm<sup>-3</sup>,  $R1 = 6.26\%$ . Structure was solved by direct methods, and refined against  $F^2$ .<sup>[13]</sup> Structures were visualised using Mercury2.0.<sup>[14]</sup>

*High pressure single crystal X-ray study of h5-II:* Phase h5-II was obtained at high pressure by loading pyridine-h<sub>5</sub> into a Merrill-Bassett diamond anvil cell,<sup>[15]</sup> and then applying enough pressure to solidify the sample into a polycrystalline mass. The pressure was reduced to just above the melting pressure, and the cell was heated until just one small seed crystal remained, and the apparatus then allowed to cool to room temperature. Data were collected and reduced according to previously published procedures.<sup>[16]</sup> Crystal data for h5-II at 1.1 GPa (measured by ruby fluorescence) in  $P2_12_12_1$ .  $a = 5.4136(8)$ ,  $b = 6.8001(17)$ ,  $c = 11.425(3)$  Å,  $V = 413.95(16)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_{\text{calc}} = 1.269$  g cm<sup>-3</sup>,  $R1 = 6.78\%$ . The structure was solved by direct methods and refined against  $F^2$  using all data with atoms modelled with isotropic displacement parameters.

*Low-temperature neutron powder diffraction study of d5:* Time-of-flight neutron powder diffraction data were recorded over the  $d$ -spacing range of 0.6–2.6 Å at backscattering ( $\langle 2\Theta \rangle = 168^\circ$ ) on the HRPD instrument at the ISIS Facility using a vanadium-tailed helium-flow orange cryostat. Coordinates for phase-I were taken from ref [2]; those for phase-II were determined from the single crystal X-ray data.

Data for d5-I at 5 K in  $Pna2_1$ :  $a = 17.24296(5)$ ,  $b = 8.88178(3)$ ,  $c = 11.22288(3)$  Å,  $V = 1718.76(1)$  Å<sup>3</sup>,  $Z = 16$ ,  $D_{\text{calc}} = 1.300$  g cm<sup>-3</sup>,  $R_{\text{wp}} = 2.97\%$ ,  $S = 1.75$ . Data for d5-II at 195 K in  $P2_12_12_1$ :  $a = 5.64729(2)$ ,  $b = 6.98010(3)$ ,  $c = 11.46507(5)$  Å,  $V = 451.94(1)$  Å<sup>3</sup>,  $D_{\text{calc}} = 1.236$  gm<sup>-3</sup>,  $R_{\text{wp}} = 1.98\%$ ,  $S = 1.23$ . The structures were refined using the Rietveld method as implemented in TOPAS-Academic.<sup>[17]</sup> The intramolecular geometry was modelled using the Z-matrix formalism assuming  $C_{2v}$  symmetry. TLS tensors were used to model the anisotropic displacement parameters.

*High pressure neutron powder diffraction study of d5:* High pressure powder diffraction of d5 was also carried out on the PEARL instrument at ISIS, with pressure applied using the Paris-Edinburgh cell; full details of these experiments will be published separately, but the transition for d5-I to d5-II was observed at 1.1 GPa.



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